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| (54) Title: BIOCHEMICALLY BALANCED PERITONEAL DIALYSIS SOLUTIONS | | | |
| (57) Abstract | | | |
| <p>A peritoneal dialysis solution that is biochemically balanced to correct metabolic acidosis associated with chronic renal failure in a more physiological manner. The peritoneal dialysis solution has a physiological pH, e.g., pH of 7.0 to 7.4, and contains bicarbonate at a concentration that is found in normal blood. Additionally, the solution contains carbon dioxide at a partial pressure that is similar to partial pressure of carbon dioxide found in normal blood. The peritoneal dialysis solution also contains a weak acid with a pKa of less than 5.0.</p> | | | |

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S P E C I F I C A T I O N

TITLE

"BIOCHEMICALLY BALANCED PERITONEAL
DIALYSIS SOLUTIONS"

5

BACKGROUND OF THE INVENTION

The present invention relates generally to peritoneal dialysis. More specifically, the present invention relates to peritoneal dialysis solutions.

10

It is known to use dialysis to support a patient whose renal function has decreased to the point where the kidneys no longer sufficiently function. Two principal dialysis methods are utilized: hemodialysis; and peritoneal dialysis.

15

In hemodialysis, the patient's blood is passed through an artificial kidney dialysis machine. A membrane in the machine acts as an artificial kidney for cleansing the blood. Because it is an extracorporeal treatment that requires special machinery, there are certain inherent disadvantages with hemodialysis.

20

To overcome the disadvantages associated with hemodialysis, peritoneal dialysis was developed. Peritoneal dialysis utilizes the patient's own peritoneum as a semi-permeable membrane. The peritoneum is the membranous lining of the abdominal cavity that due to a large number of blood vessels and capillaries is capable of acting as a natural semi-permeable membrane.

30

In peritoneal dialysis, a dialysis solution is introduced into the peritoneal cavity utilizing a catheter. After a sufficient period of time, an exchange of solutes between the dialysate and the blood is achieved. Fluid removal is achieved by providing a suitable osmotic gradient from the blood to the dialysate to permit water outflow from the blood. This allows the

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proper acid-base of electrolytes and fluid balance to be returned to the blood and the dialysis solution is simply drained from the body cavity through the catheter.

5 A number of dialysis solutions have been utilized and suggested. One of the difficulties with dialysis solutions that are used for peritoneal dialysis is that they are not ideal solutions for maintaining acid base homeostasis. Metabolic acidosis is a catabolic event that can occur in peritoneal dialysis patients.

10 In this regard, the kidneys play a major role in the maintenance of the acid-base balance. In chronic renal failure, the acid generated from the metabolism of dietary proteins can lead to metabolic acidosis. Metabolic acidosis can have a profound and acute effect 15 on the respiratory, cardiac, and/or nervous systems. Long term consequences of metabolic acidosis include protein malnutrition and skeletal diseases.

20 Lactate has been utilized in peritoneal dialysis solutions for the purpose of maintaining acid-base balance in peritoneal dialysis patients. Typical commercially available peritoneal dialysis solutions contain 35 to 40 mEq/L of lactate.

25 These solutions are adequate in maintaining acid-base balance in a number of dialysis patients. However, patients who are deficient in lactate metabolism and/or who also experience or suffer from hepatic failure or shock can develop lactic acidosis. This syndrome includes as characteristic symptoms hyperventilation, abdominal pain, and disturbances in consciousness while 30 the patient receives lactate-containing peritoneal dialysis fluids.

An additional issue with respect to lactate peritoneal dialysis solutions is that a number of in

vitro studies performed with peritoneal cells indicate that altered cell function can occur when peritoneal cells are exposed to large concentrations of lactate. These changes in cell function can compromise host defense leading to increased rates of infection and damage to the peritoneal membrane.

In order to address this issue, peritoneal dialysis solutions in which lactate is completely replaced by bicarbonate have been proposed. However, in order to balance total body hydrogen ion content against metabolically generated hydrogen, and to maintain normal plasma carbonic acid and bicarbonate concentrations, it is necessary to use bicarbonate concentrations that are considerably in excess of normal. In this regard, bicarbonate concentration upwards of 38 mM/L are believed to be necessary.

Because it is necessary to maintain the solution at a physiological pH, the requirement of such a high bicarbonate solution requires a partial pressure of carbon dioxide (pCO_2) that is at least twice the physiologic pCO_2 (e.g., greater than 80 mmHg). Although such a solution may meet the metabolic needs of the patient, such a solution does not provide a physiological environment for the peritoneal cells in contact with the solution. Due to the differences in transport rates between bicarbonate and carbon dioxide, with such a solution, the intracellular hydrogen ion concentration of the cell's lining the peritoneal cavity, as well as those present in the peritoneal cavity, would be severely low placing them at a metabolic disadvantage. This metabolic disadvantage will increase more than would be expected if they share the extracellular environment f normal pH, but a supernormal bicarbonate and pCO_2 .

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There is therefore a need for a peritoneal dialysis solution that adequately addresses the problem of metabolic acidosis associated with end stage renal disease.

5

SUMMARY OF THE INVENTION

The present invention provides a peritoneal dialysis solution that is biochemically balanced to correct metabolic acidosis associated with chronic renal failure in a more physiological manner. The peritoneal dialysis solution has a physiological pH, e.g., pH of 7.0 to 7.4, and contains bicarbonate at a concentration that is found in blood involved in diffusive transport of solutes with dialysis fluid. This will block the loss of bicarbonate during peritoneal dialysis which is the case with present solutions. Additionally, the solution contains carbon dioxide at a partial pressure that is similar to partial pressure of carbon dioxide found in the blood capillaries. The peritoneal dialysis solution also contains a weak acid with a pKa of less than 5.0 at an amount needed to neutralize acid generated from endogenous metabolism. These weak acids are also the normal biochemical intermediates of glucose metabolism resulting in neutral end products.

To this end, the present invention provides a peritoneal dialysis solution including bicarbonate at a level of less than or equal to 30 mM/L, having a PCO₂ that is less than 60 mmHg, and including at least one weak acid selected from the group consisting of: lactate; pyruvate; citrat ; isocitrate; cis-aconitase; α-ketoglutarate; succinate; fumarat ; malate; and oxaloacetate.

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In an embodiment of the peritoneal dialysis solution, bicarbonate is present in the solution at 25 mM/L.

5 In an embodiment of the peritoneal dialysis solution, the weak acid is present in an amount comprising approximately 10 mEq/L to about 20 mEq/L.

In an embodiment of the peritoneal dialysis solution, the PCO_2 of the solution is approximately the same as the PCO_2 of blood.

10 In an embodiment of the peritoneal dialysis solution, the solution has a pH of approximately 7.4.

In an embodiment of the peritoneal dialysis solution, the weak acids have a pKa of < 5.0.

15 In another embodiment, the present invention provides a peritoneal dialysis solution comprising:

| | |
|---------------------------|-----------|
| Dextrose (hydrous) (g/dL) | 1.5-4.25 |
| Sodium (mEq/L) | 100-140 |
| Chloride (mEq/L) | 70-110 |
| Calcium (mEq/L) | 0.0-4.0 |
| 20 Magnesium (mEq/L) | 0.0-4.0 |
| Bicarbonate (mEq/L) | 20.0-30.0 |
| Weak acid (mEq/L) | 10.0-20.0 |

25 wherein the weak acid is chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α -ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

In an embodiment, the solution includes an osmotic agent other than dextrose.

30 In an embodiment, the present invention provides a method for correcting metabolic acidosis in a dialysis patient suffering or likely to suffer from same comprising the step of administering to a dialysis patient a peritoneal dialysis solution that has a

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bicarbonate level and carbon dioxide partial pressure that is substantially similar to that found in the normal person's blood.

5 An advantage of the present invention is that it provides an improved peritoneal dialysis solution.

Another advantage of the present invention is that it provides bicarbonate to the patient when blood bicarbonate is below normal.

10 Still an advantage of the present invention is that it removes bicarbonate when blood bicarbonate is above normal.

Another advantage of the present invention is that it provides a biochemically balanced peritoneal dialysis solution.

15 Furthermore, an advantage of the present invention is that it provides a peritoneal dialysis solution that corrects metabolic acidosis associated with end stage renal disease.

20 Moreover, an advantage of the present invention is that it provides a peritoneal dialysis solution that balances bicarbonate at a normal concentration with a PCO_2 at normal partial pressure.

25 Further, an advantage of the present invention is that the dialysis solution provides an additional contribution of bicarbonate by diffusion of bicarbonate to offset the end balance of the metabolic hydrogen load and vice versa for a supernormal concentration.

30 Another advantage of the present invention is that it provides a peritoneal dialysis solution at a physiological pH.

Additional features and advantages of the present invention are described in, and will be apparent from,

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the detailed description of the presently preferred embodiments.

DETAILED DESCRIPTION

OF THE PRESENTLY PREFERRED EMBODIMENTS

The present invention provides improved peritoneal dialysis solutions. The solutions are biochemically balanced to correct metabolic acidosis that is associated with chronic renal failure. Pursuant to the present invention, the solutions are biochemically balanced in a more physiological manner than prior peritoneal solutions.

To this end, the present invention provides peritoneal dialysis solutions that contain bicarbonate at a more physiological level, e.g., at a level substantially equivalent to that found in normal blood.

The peritoneal dialysis solution of the present invention, in an embodiment, includes bicarbonate present at a level of approximately 20 mM/L to about 30 mM/L. In a most preferred embodiment, bicarbonate is present at a level of 25 mM/L.

Additionally, the solution contains carbon dioxide at a partial pressure that is less than 60 mmHg. In a preferred embodiment the pCO₂ of the solution is similar to the partial pressure of carbon dioxide found in blood capillaries.

Further, preferably, the dialysis solutions have a pH of 7.4. Therefore, the solution, although balanced biochemically, is a physiologically acceptable solution.

Additionally, the solutions include a weak acid with a pKa of less than 5. These weak acids are chosen so as to be normal biochemical intermediates of glucose metabolism. Preferably, the weak acids are chosen from

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the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α -ketoglutarate; succinate; fumarate; malate; and oxaloacetate. These acids can be present either alone or in combination in the solution.

5 Preferably, the weak acids are present at a level of approximately 10 to about 20 mEq/L. Preferably, the weak acid are present mainly as sodium salts. The weak acid is present in an amount that would offset the daily metabolic hydrogen production of approximately 1

10 mEq/kg/day.

Pursuant to the present invention, any osmotic agent can be used in the solution. For example, dextrose, maltodextrin, glycerol, polyglucose, polypeptides and amino acids can be used as the osmotic agent.

15 Preferably, the peritoneal dialysis solution, if it contains dextrose as an osmotic agent, has a general composition such as that set forth below:

| | | |
|----|---------------------------|-----------|
| | Dextrose (hydrous) (g/dl) | 1.5-4.25 |
| | Sodium (mEq/L) | 100-140 |
| 20 | Chloride (mEq/L) | 70-110 |
| | Calcium (mEq/L) | 0.0-4.0 |
| | Magnesium (mEq/L) | 0.0-4.0 |
| | Bicarbonate (mEq/L) | 20.0-30.0 |
| | Weak acid (mEq/L) | 10.0-20.0 |
| 25 | pH | 7.0-7.4 |

Preferably, solutions containing an osmotic agent other than dextrose composition have the general composition:

| | | |
|----|----------------------|---------|
| | Osmotic agent (mM/L) | 1-200 |
| 30 | Sodium (mEq/L) | 100-140 |
| | Chloride (mEq/L) | 70-110 |
| | Calcium (mEq/L) | 0.0-4.0 |
| | Magnesium (mEq/L) | 0.0-4.0 |

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| | |
|---------------------|-----------|
| Bicarbonate (mEq/L) | 20.0-30.0 |
| Weak Acid (mEq/L) | 10-20.00 |
| pH | 7.0-7.4 |

5 The peritoneal dialysis solutions of the present invention balance bicarbonate at normal concentrations and have a pCO_2 at normal partial pressure. The weak acid under usual circumstances will have an infinite gradient from dialysate to blood. Thus, the weak acid can be expected to perform in a relatively predictable 10 manner in correcting the metabolic acidosis of chronic uremia.

15 Due to the composition of the present invention, should the patient's bicarbonate level drop below prescribed normal blood figure of 25 mM/L, then there will be an additional contribution by diffusion of bicarbonate to offset the unbalanced metabolic hydrogen load and vice versa for a supernormal concentration. Phrased in a different manner, the solution has a built 20 in servo mechanism around the figure of 25 mM/L for bicarbonate. A pure bicarbonate solution at higher than normal concentrations does not offer this benefit.

25 By way of example, and not limitation, examples of specific peritoneal dialysis solutions of the present invention will now be given.

25

EXAMPLE NO. 1

| | |
|---------------------------|-------|
| Dextrose (hydrous) (g/dl) | 1.5 |
| Sodium (mEq/L) | 132 |
| Chloride (mEq/L) | 96 |
| Calcium (mEq/L) | 3.5 |
| Magnesium (mEq/L) | 0.5 |
| Bicarbonat (mEq/L) | 25.00 |
| Lactate (mEq/L) | 15 |
| pH | 7.4 |

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EXAMPLE NO. 2

| | | |
|---|---------------------------|-------|
| | Dextrose (hydrous) (g/dl) | 2.5 |
| | Sodium (mEq/L) | 132 |
| | Chloride (mEq/L) | 96 |
| 5 | Calcium (mEq/L) | 3.5 |
| | Magnesium (mEq/L) | 0.5 |
| | Bicarbonate (mEq/L) | 25.00 |
| | Lactate (mEq/L) | 15.0 |
| | pH | 7.4 |

EXAMPLE NO. 3

| | | |
|----|---------------------------|-------|
| 10 | Dextrose (hydrous) (g/dl) | 4.25 |
| | Sodium (mEq/L) | 132 |
| | Chloride (mEq/L) | 96 |
| | Calcium (mEq/L) | 3.5 |
| 15 | Magnesium (mEq/L) | 0.5 |
| | Bicarbonate (mEq/L) | 25.00 |
| | Lactate (mEq/L) | 15.0 |
| | pH | 7.4 |

EXAMPLE NO. 4

| | | |
|----|---------------------------|-----|
| 20 | Dextrose (hydrous) (g/dl) | 1.5 |
| | Sodium (mEq/L) | 132 |
| | Chloride (mEq/L) | 96 |
| | Calcium (mEq/L) | 3.5 |
| | Magnesium (mEq/L) | 0.5 |
| 25 | Bicarbonate (mEq/L) | 20 |
| | Lactate (mEq/L) | 20 |
| | pH | 7.4 |

EXAMPLE NO. 5

| | | |
|----|---------------------------|------|
| 30 | Dextrose (hydrous) (g/dl) | 2.25 |
| | Sodium (mEq/L) | 132 |
| | Chloride (mEq/L) | 96 |
| | Calcium (mEq/L) | 3.5 |
| | Magnesium (mEq/L) | 0.5 |

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| | | |
|--|---------------------|------|
| | Bicarbonate (mEq/L) | 20.0 |
| | Lactate (mEq/L) | 20.0 |
| | pH | 7.4 |

EXAMPLE NO. 6

| | | |
|----|---------------------------|------|
| 5 | Dextrose (hydrous) (g/dl) | 4.25 |
| | Sodium (mEq/L) | 132 |
| | Chloride (mEq/L) | 96 |
| | Calcium (mEq/L) | 3.5 |
| | Magnesium (mEq/L) | 0.5 |
| 10 | Bicarbonate (mEq/L) | 20 |
| | Lactate (mEq/L) | 20 |
| | pH | 7.4 |

EXAMPLE NO. 7

| | | |
|----|---------------------------|------|
| 15 | Dextrose (hydrous) (g/dl) | 1.5 |
| | Sodium (mEq/L) | 132 |
| | Chloride (mEq/L) | 96 |
| | Calcium (mEq/L) | 3.5 |
| | Magnesium (mEq/L) | 0.5 |
| | Bicarbonate (mEq/L) | 30.0 |
| 20 | Lactate (mEq/L) | 10.0 |
| | pH | 7.4 |

EXAMPLE NO. 8

| | | |
|----|---------------------------|------|
| 25 | Dextrose (hydrous) (g/dl) | 2.50 |
| | Sodium (mEq/L) | 132 |
| | Chloride (mEq/L) | 96 |
| | Calcium (mEq/L) | 3.5 |
| | Magnesium (mEq/L) | 0.5 |
| | Bicarbonate (mEq/L) | 30.0 |
| | Lactate (mEq/L) | 10.0 |
| 30 | pH | 7.4 |

EXAMPLE NO. 9

| | | |
|--|---------------------------|------|
| | Dextrose (hydrous) (g/dl) | 4.25 |
| | Sodium (mEq/L) | 132 |

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| | | |
|---|---------------------|------|
| | Chloride (mEq/L) | 96 |
| | Calcium (mEq/L) | 3.5 |
| | Magnesium (mEq/L) | 0.5 |
| | Bicarbonate (mEq/L) | 30.0 |
| 5 | Lactate (mEq/L) | 10.0 |
| | pH | 7.4 |

It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present invention and without diminishing its attendant advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

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WE CLAIM:

1. A peritoneal dialysis solution including bicarbonate at a level of greater than or equal to 20 mM/L and less than or equal to 30 mM/L, having a carbon dioxide partial pressure that is less than 60 mmHg and including at least one weak acid present in an amount comprising approximately 10 mEq/L to about 20 mEq/L selected from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α -ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

2. The peritoneal dialysis solution of Claim 1 wherein bicarbonate is present in the solution at 25 mM/L.

3. The peritoneal dialysis solution of Claim 1 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of blood.

4. The peritoneal dialysis solution of Claim 1 wherein the solution has a pH of approximately 7.0 to about 7.4.

5. The peritoneal dialysis solution of Claim 1 wherein the weak acids have a pKa of < 5.0.

6. The peritoneal dialysis solution of Claim 1 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of blood.

7. A peritoneal dialysis solution comprising:

| | |
|---------------------------|----------|
| Dextrose (hydrous) (g/dl) | 1.5-4.25 |
| Sodium (mEq/L) | 100-140 |
| Chlorid (mEq/L) | 70-110 |
| Calcium (mEq/L) | 0.0-4.0 |
| Magnesium (mEq/L) | 0.0-4.0 |

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| | | |
|--|---------------------|-----------|
| | Bicarbonate (mEq/L) | 20.0-30.0 |
| | Weak acid (mEq/L) | 10.0-20.0 |

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; 5 isocitrate; cis-aconitase; α -ketoglutarate; succinate; fumarate; malate; and oxaloacetate.

8. The peritoneal dialysis solution of Claim 7 wherein the solution has a pH of approximately 7.0 to about 7.4.

10 9. The peritoneal dialysis solution of Claim 7 wherein the weak acids have a pKa of < 5.0.

10. The peritoneal dialysis solution of Claim 7 wherein the carbon dioxide partial pressure is less than 60 mmHg.

15 11. The peritoneal dialysis solution of Claim 7 wherein the carbon dioxide partial pressure of the solution is approximately the same as the carbon dioxide partial pressure of normal blood.

12. A peritoneal dialysis solution comprising:

| | | |
|----|---------------------------|-----------|
| 20 | Dextrose (hydrous) (g/dl) | 1.5-4.25 |
| | Sodium (mEq/L) | 100-140 |
| | Chloride (mEq/L) | 70-110 |
| | Calcium (mEq/L) | 0.0-4.0 |
| | Magnesium (mEq/L) | 0.0-4.0 |
| 25 | Bicarbonate (mEq/L) | 20.0-30.0 |
| | Weak acid (mEq/L) | 10.0-20.0 |

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; α -ketoglutarate; succinate; 30 fumarate; malate; and oxal acetate; and

the solution has a carbon dioxide partial pressur that is substantially similar to the carbon di xide

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partial pressure of a normal subject's blood and the solution has a pH of 7.0 to 7.4.

13. A method for correcting metabolic acidosis in a dialysis patient suffering or likely to suffer from
5 same comprising the step of:

administering to a patient a peritoneal dialysis solution that has a bicarbonate level and carbon dioxide partial pressure that are substantially similar to that found in the patient's blood.

10 14. The method of Claim 13 wherein the solution comprises:

| | | |
|----|---------------------------|-----------|
| | Dextrose (hydrous) (g/dl) | 1.5-4.25 |
| | Sodium (mEq/L) | 100-140 |
| | Chloride (mEq/L) | 70-110 |
| 15 | Calcium (mEq/L) | 0.0-4.0 |
| | Magnesium (mEq/L) | 0.0-4.0 |
| | Bicarbonate (mEq/L) | 20.0-30.0 |
| | Weak acid (mEq/L) | 10.0-20.0 |

15 16. The method of Claim 13 including the step of administering to the patient a weak acid that is present in the solution in an amount that offsets the daily hydrogen production of approximately 1 mEq/kg/day.

20 17. The method of Claim 14 wherein the weak acids have a pKa of < 5.0.

25 18. The method of Claim 13 wherein the solution does not include lactate.

30 19. The method of Claim 15 wherein the weak acid is present in the solution at a level of approximately 10 to about 20 mEq/L.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/06784

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K33/14 A61M1/16 A61M1/28 // (A61K33/14, 33:10, 33:00,
31:70, 31:19)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | EP, A, 0 399 549 (FRESENIUS AG) 28 November 1990 see the whole document ----- | 1-19 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| | |
|---|--|
| Date of the actual completion of the international search | Date of mailing of the international search report |
| 10 October 1995 | 27. 10. 95 |
| Name and mailing address of the ISA | Authorized officer |
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016 | Leherte, C |

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US 95/06784**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 13-19 because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claims 13-19 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat'l Application No

PCT/US 95/06784

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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